Environmental Health Perspectives
Vol. 74, pp. 11-13, 1987

Introduction: Biological Markers of Male Reproductive Toxicology

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Reproduction is a complex, stepwise series of processes that begins with gametogenesis, continues through gamete interaction, implantation, embryonic development, growth, parturition, and postnatal adaptation, and is completed with the development and sexual maturation of the newly formed organism. These reproductive processes do not take place in a chemically pristine environment, but rather in an environment increasingly contaminated with the products and by-products of the chemical age in which we live. Some environmental pollutants are known to be carcinogenic, mutagenic, or toxic to the reproductive system, but most have not been adequately tested for reproductive toxicity.

Just as reproduction is complex, biological mechanisms underlying toxicology are similarly complex and involve absorption, distribution, metabolism (toxification and/or detoxification), excretion, and repair. The synthesis of these sciences into the relatively nascent science of reproductive toxicology includes teratology, pharmacology, epidemiology, and occupational and environmental health.

Female reproductive function (especially pregnancy outcome) has historically been the focus of attention, but there is increasing interest in the effects of chemical exposure on male reproductive function. Several reports have documented the physiology, biochemistry, and toxicology of male mammalian reproduction, and evaluated susceptibility of the male to the effects of exogenous chemicals (*1–6*).

The differences between male and female in reproductive anatomy and biologic mechanisms are important factors in reproductive toxicology. The structures and processes that are involved in male reproductive function and that might be influenced directly or indirectly by exogenous chemicals include the hypothalamic-pituitary-gonadal axis, testes, efferent ducts, epididymides and male accessory organs, formation and composition of semen, sexual behavior, and the processes of erection and ejaculation. Because of the easier accessibility of gametes and gonads in the male, more xenobiotic compounds tested for toxicity have been shown to be toxic to male reproductive processes than to female reproductive processes. It is not known whether that difference reflects an actual gender difference in gonadal or gamete toxicity or is simply an artifact of experimental convention. For example, more characteristics are available for scoring sperm (e.g., shape, motility, and penetrability) than for scoring oocytes, which are more difficult to obtain.

Another critical issue in reproductive toxicity is the window of sensitivity, or the time during which toxicity occurs. This has been demonstrated on many occasions in studies of teratogens and toxins acting on spermatogenesis. Several studies have demonstrated that some compounds are toxic to the developing ovary, but have no effect on the developed ovary (*7,8*); the issue of differential follicular or oocyte sensitivity has seldom been similarly explored. A few experimental and clinical studies have attempted to explore the effects of age on gonadal sensitivity to chemotherapeutic agents or other xenobiotic compounds (*7,8*).

Obviously, reproduction is essential to the continued existence of any species. It is therefore necessary to understand reproductive toxins and their mechanisms and sites of action and to learn about species (especially human) susceptibility to them. General aspects of testicular toxicity (*9,10*) and ovarian toxicity (*7,8,11*) have been addressed. Several recent reviews dealt with general aspects of reproductive toxicology (*1,7*) and gonadal metabolism (*12*). An ever-expanding literature is devoted to teratology (*13–17*). Reproductive effects of occupational exposures have been considered (*18–21*). Several reviews have addressed issues of comparative reproductive biology (*22–26*).

The mechanisms of toxicity can be reduced ultimately to some effect that interrupts the normal functioning of a cell, tissue, organ, or organism (*27*). Toxicants act to interrupt the flow of matter, energy, or information that is necessary for normal functioning of cells, tissues, organs, or organisms (Fig. 1). After exposure to a reproductive toxin, it must be distributed to the target organ (gonad, hypothalamus, pituitary, uterus, epididymis, liver, etc.) if it is to exert its adverse effect. If the compound is metabolized and cleared, no adverse effect will occur. Within the target organ, the toxin interacts

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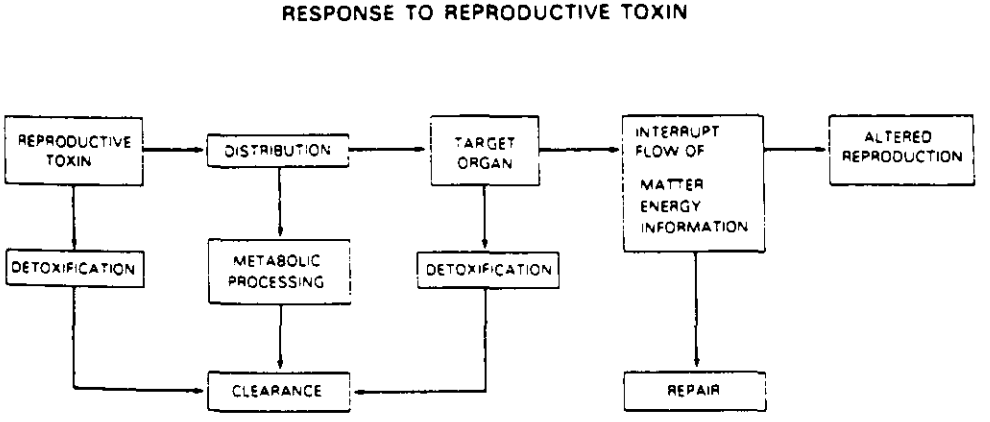

FIGURE 1. The response of an organism to a reproductive toxin is complex and involves distribution, detoxification, clearance, and possibly, repair before the adverse effect is produced. If the multistep defense network of the organism is unable to block the toxic interruption of the flow of matter, energy, or information necessary for normal reproduction, impaired function will result. From Mattison (*5*).

with a critical cell or subcellular component and thus disrupts an event necessary for normal reproductive function. If the effect of the interaction is not repaired, the toxic effect, altered reproduction, is expressed. The effect can be very specific, and concern only a single function of a single cell type, or it can be broad and nonspecific and concern multiple sites of toxicity in the organism. Within each target, however, the process must be completed for reproductive toxicity to be said to occur.

Some reproductive toxins act directly either by virtue of structural similarity to endogenous compounds (e.g., hormones and nutrients) or by virtue of chemical reactivity (e.g., alkylating agents, denaturants, and chelators). Other reproductive toxins act indirectly and require metabolic processing in the organism or organ to bring about a toxic effect; a metabolite formed can then exert its toxic effect through one of the direct mechanisms of reproductive toxicity described (structural similarity or chemical reactivity). Other indirectly acting reproductive toxins act by producing alterations in physiologic control mechanisms (e.g., enzyme induction or inhibition).

It is also possible for a given reproductive toxin to exert adverse effects through more than one mechanism. For example, the halogenated polycyclic hydrocarbons, such as polychlorinated or polybrominated biphenyls, can act indirectly by induction of microsomal monooxygenases or transferases and directly by virtue of steroid hormone agonist properties.

As discussed in the introductory article from the Committee on Biological Markers (*28*), the objective of the new field of biologic markers is to identify toxic effects, exposures, and susceptibilities with improved sensitivity and accuracy of predicting responses in the organism. In this regard, the first section of this symposium addressed biologic markers in male reproductive toxicology.

Curtis Chubb's section, titled "Animal Models of Physiologic Markers of Male Reproduction: Genetically Defined Infertile Mice," describes attempts to identify reproductive defects in mice which have single-gene mutations that induce infertility. This section includes flow charts showing how biologic markers have been applied and a suggested sequence for future applications.

Eugene Rinchik's section, titled "Molecular Analysis of Heritable Mouse Mutations," discusses the nature and effects of a complex set of radiation-induced mutations and their translation into specific phenotypes. The characterization of the mice has lead to an increased understanding of the process of spermatogenesis. With this increased understanding, the possible targets of toxic action can be understood.

Mortimer Mendelsohn's section, titled "Biomarkers in the Detection of Human Heritable and Germinal Mutagenesis," discusses the detection of induced mutational events in offspring and germ cells of exposed individuals. Finally, Norman Hecht's section, titled "Detecting the Effects of Toxic Agents on Spermatogenesis with DNA Probes," discusses the application of molecular biology to the study of mammalian testicular differential and the regulation of germ cell formation. Recombinant DNA techniques used to measure the effects of toxic agents on testicular cells is discussed.

This symposium represents an attempt to review and synthesize those diverse sciences, with a focus on biologic markers that might be used to identify susceptibilities, exposures, and preclinical health effects. As knowledge and understanding continue to grow in this new field of biologic markers, the public-health benefit becomes more apparent.

The authors thank Andrew Pope of the National Research Council for his assistance with this paper.

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